

REMARKS

I. Introduction

An earlier office action dated July 30, 2007, prompted a telephone conversation between the Examiner and Applicants' undersigned attorney on August 21, 2007, concerning an errant requirement for restriction set forth in the action. The present non-final action resulted from that discussion, setting forth a revised requirement for restriction, an action on the merits, and a new time period for reply. Applicants now request reconsideration of the application in view of the accompanying declaration and the comments below.

II. Restriction and Status of the Claims

The PTO required restriction between three (3) groups of claims:

- I. Claims 3, 6-12, and 23 drawn to compounds;
- II. Claims 14, 17, and 28 drawn to methods of use; and
- III. Claims 24, 26, and 27 drawn to a process.

Applicants affirm their **election of Group I**, made during the telephone call on August 21, 2007.

Applicants previously cancelled claims 1, 2, 4, 5, 13, 15, 16, and 18-22. In response to Applicants' election, the PTO withdrew claims 14, 17, and 24-28 from consideration. No claims are presently cancelled.

Claims 6-12, and 23 are amended to clarify the scope of "functionalized" substituents. After entry of the amendments, claims 3, 6-12, 14, 17, and 23-28 will be pending, and claims 3, 6-12, and 23 are examined on the merits.

III. The Office Action

Applicants gratefully acknowledge the PTO's allowance of claim 3. Office Action at page 5.¹ At issue are new grounds for rejections, which Applicants address below in the order presented in the Office Action.

A. Rejection of Claims Under 35 U.S.C. § 101

The PTO rejected claim 6 for alleged want of an asserted utility or a well established utility. Office Action at page 5. In support of the rejection, the PTO advanced the dual proposition that the claimed spiroacetal compounds (1) "cannot be converted to Peloruside A (*id.* at 5) or (2) "would not function in the same manner as Peloruside A" (*id.* at 6). Largely relying upon the cited Jimenez-Barbero and Pineda publications, the PTO reasoned that the spiroacetal at C-9 and C-11 would conformationally restrict the macrocycle ring in Peloruside A, manifesting a "drastic change" in the conformation that is "critical . . . for the molecule to interact with tubulin." *Id.* at 8. Applicants respectfully traverse this ground for rejection.

What the PTO failed to articulate is any reason, credible or otherwise, why such conformational restriction would result in a "drastic change" or *abolish* activity of the claimed compounds. Applicants already have ascribed therapeutic utility to the claimed compounds, and so the mere mention that conformational changes in the macrocycle can affect activity is no reason to doubt such utility.

The accompanying declaration by co-inventor Jef DeBrabander ("the declaration") explains, moreover, how the claimed spiroacetal compounds *lock the macrocycle into the active conformation*. The declarant explains in this regard that the hydroxyl groups at C-9 and C-11 in peloruside A are positioned so as to engage in hydrogen bonding, thereby enforcing the presence of a six-membered ring. The claimed spiroacetal compounds explicitly feature such a ring; hence, they likewise constrain the macrocycle into the conformation that exists in active peloruside A. Because the claimed compounds and peloruside A share nearly identical structures, there is every reason for the claimed compounds to exhibit similar therapeutic activity satisfying the strictures of the utility

¹ The Office Action dated July 30, 2007, and the present Office Action each state that claim 3 is allowed. Yet the present Office Action summary indicates that claim 3 is rejected. While Applicants believe that this designation is in error, and certainly at odds with the text of the Office Action, they would appreciate the PTO simply clarifying the status of claim 3.

requirement under section 101. For these reasons, Applicants respectfully urge to withdraw the rejection.

B. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

The PTO rejected claim 4-12 and 23 for an alleged want of enablement in relation to certain compounds. Office Action at 10. In particular, the PTO presented essentially three reasons in support of the rejection.

First, the PTO decried cyclopropyl compounds of claims 9-12 and 23 because the PTO could not identify the source of necessary precursor compounds it designated as "A" and "B," specifically asking "[w]here . . . the directions to prepare or buy them [may] be found." *Id.* at 12-13. Second, the PTO flatly discredited the reaction scheme proposed in Figure 90 as a plausible synthetic route to compounds lacking substituents OR₄ and OR₆ because the olefin in intermediate compound 61F would undergo unwanted dihydroxylation and subsequent cleavage under the conditions prescribed for the synthesis of the claimed compounds. Finally, the PTO characterized as "disturbing" the "laundry list" of possible substituents for R⁸, supposing their introduction into the claimed compounds *via* aldol reactions too great of a challenge for the skilled artisan. *Id.* at 15. For the reasons detailed below, Applicants respectfully traverse the rejection inasmuch as it might apply to the claims as amended.

The accompanying declaration should dispel each of the PTO's stated concerns, as summarized above. For instance, intermediate cyclopropyl compounds "A" and "B" are readily prepared *via* known literature compounds and alcohol protecting methodologies that require no more than the most basic skill in organic synthesis (declaration at para. 11).

Further, concerning intermediate 61F, the declarant elaborates on the chemical difference between reactive terminal olefins and relatively unreactive internal olefins. Specifically, the *internal* olefin in intermediate 61F remains untouched under synthesis conditions prescribed for the manufacture of the claimed compounds lacking OR₄ and OR₆ substituents (declaration at para. 12).

Finally, structural diversity at R⁸ does not present the challenges supposed by the PTO. On the contrary, the skilled artisan knows that the requisite aldol reaction and the enolate reactant are amenable to rich variation at R⁸ (declaration at para. 13). Peripheral modifications, moreover, to the peloruside A macrocycle would not be expected to significantly impact therapeutic potential of the compounds, for the reasons concerning the more critical preservation of the macrocycle conformation

discussed above. Having now advanced credible and factual reasons supporting the enablement of the full scope of the claimed invention, Applicants courteously urge the PTO to reconsider and withdraw this rejection.

C. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The PTO rejected claims 6-23 for alleged indefiniteness in the recitation of certain “functionalized” groups. Office Action at page 3. In support of the rejection, the PTO asserted an “inability to ascertain what this functionalization is,” specifically how the specified groups are functionalized. *Id.*

While the claims delineate what is intended by such functionalization, Applicants amended them to clarify that the functionalized groups bear halide, aryl, or heteroaryl substituents. Applicants therefore request withdrawal of this rejection.


* * *

Applicants believes that the present application is now in condition for allowance. To that end, they respectfully request favorable reconsideration of the application as amended. Examiner O'Dell is invited to contact Applicants' undersigned attorney by telephone if he believes that any remaining concerns warrant a telephone interview.

Respectfully submitted,

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By



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The Commissioner is hereby authorized to charge any additional fees, which may be required regarding this application under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If an extension of time is needed for timely acceptance of submitted papers, Applicants hereby petition for such extension under 37 CFR §1.136 and authorize payment of the relevant fee(s) from the deposit account.